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| APPLICATION NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTORNEY DOCKET NO. |
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| 08/692,084 | 08/08/96 | RODRIGUEZ M | 1199-1-001-C |

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DAVID A JACKSON
KLAUBER AND JACKSON
411 HACKENSACK AVENUE
HACKENSACK NJ 07601

| EXAMINER | |
|---|---|
| DUFFY, P | |
| **ART UNIT** | **PAPER NUMBER** |
| 1818 | 9 |

**DATE MAILED:** 10/02/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

## OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 6-19-97.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) 1-20 is/are pending in the application.

Of the above, claim(s) 5-8 and 15-18 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-4, 9-14 and 19 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims 1-20 are subject to restriction or election requirement.

**Application Papers**

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 8, mailed 5/7/97

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

## DETAILED ACTION

### *Priority*

1. Applicant's are requested to update the US application for which this application claims priority to under § 120.

### *Information Disclosure Statement*

2. The information disclosure statement filed May 7, 1997 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The references which were not initialed by the examiner have not been considered because a copy was not available.

### *Drawings*

3. The drawings submitted with this application were declared informal by applicant. Accordingly they have not been reviewed by a draftsperson at this time. When formal drawings are submitted, the draftsperson will perform a review. Direct any inquires concerning drawing review to the Drawing Review Branch (703) 305-8404.

### *Election/Restriction*

4. Applicant's election with traverse of Group I in Paper No. 7, mailed 6/19/97 is acknowledged. The traversal is on the ground(s) that the search burden is not undue because it would not be undue to examine different methods because they use the same antibody

composition. This is not found persuasive because the methods are distinct and would require separate searches thus it would be an undue search burden to examine all inventions of the application. As to the same class/subclass search, applicants remarks are not persuasive because completely different inventions can be presented in the same class/subclass designation. Moreover, applicant is entitled to a single patent for a single invention. Since the methods are directed to different inventions and the search for remyelination would not encompass proliferation, the search would be undue and applicants arguments are not persuasive.

The requirement is still deemed proper and is therefore made FINAL.

5. Claims 5-8 and 15-18 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 7, mailed 6-19-97.

***Double Patenting***

6. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

7. Claim 19 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1 of prior U.S. Patent No. 5,591,629 this is a double patenting rejection. Claim 19, is drawn to a pharmaceutical composition comprising monoclonal antibodies selected from the group consisting of SCH94.03 and others. Applicant has already received a patent for the composition of the monoclonal antibody SCH94.03, deposited as ATCC accession number CRL 11627. The pharmaceutical composition recites intended use only and does not differentiate the markush species from that for which applicant has already received a patent.

8. Claims 1-4, 9-14 and 19 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-4, 9-14 and 19 of copending Application No. 08/779,784. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

### *Claim Rejections - 35 USC § 101*

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

10. Claim 19 is rejected under 35 U.S.C. 101 because: the claim recites "natural autoantibody", thus it appears that this is a product of nature and thus the claimed invention is directed to non-statutory subject matter.

### *Claim Rejections - 35 USC § 112*

11. Claims 1-4, 9-14 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of stimulating remyelination in mice or by administering to the mouse an effective amount of the monoclonal antibody SCH94.03 or

SCH94.32, it does not reasonably provide enablement for methods of stimulating remyelination in humans or treatment of a demyelinating disease in mice or humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As to claims 1-4, 9-14, and 19, the specification lacks complete deposit information for the deposit of SCH94.03, SCH79.08, 01, 04, A2B5, HNK-1. Because it is not clear that cell lines producing the monoclonal antibodies possessing the properties of the above recited antibodies are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the best mode disclosed by the specification requires the use of 01, 04, A2B5, HNK-1, a suitable deposit for patent purposes is required. Accordingly, filing of evidence of the reproducible production of the cell line producing the monoclonal antibody claimed in claims 1-4, 9-14 and 19, is required. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the cell line is an unpredictable event.

Applicant's referral to the deposit of the hybridoma cell lines SCH94.03, SCH79.08 on pages 2-3 of the specification is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR §1.801-1.809 have been met.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application ***and that the deposit will***

***be replaced if viable samples cannot be dispensed by the depository is required.*** This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of deposit and the complete name and full street address of the depository is required.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR §1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

© the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

In addition, a deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological material not made under the Budapest Treaty must be filed in the application and must contain:

1) The name and address of the depository;
2) The name and address of the depositor;
3) The date of deposit;
4) The identity of the deposit and the accession number given by the depository;
5) The date of the viability test;
6) The procedures used to obtain a sample if the test is not done by the depository; and
7) A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the hybridoma cell line described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR §1.801-1.809 for further information concerning deposit practice.

As to claims 1-4 and 9-14, the specification is not enabled for stimulating remyelination of central nervous system axons or treatment of demyelinating disease of the central nervous system in any mammal with the exception of a mouse for the foregoing reasons. The prior art establishes that for demyelinating diseases in general, the currently employed mouse models of the specification (Experimental Autoimmune Encephalomyelitis and Theiler's Virus-induced Demyelinating Disease) do not predictably and reproducibly correlate with therapeutic effectiveness in the human species. Applicants have heavily relied on evidence from *in vitro* and *in vivo* murine model data including the Theiler's Virus-induced demyelinating Disease and the

Experimental Autoimmune Encephalomyelitis (EAE) model for multiple sclerosis and other demyelinating diseases in humans and other mammals. That rodent (i.e. murine) animal models lack sufficient correlation with human disease is specifically addressed in Raines (Handbook of Clinical Neruology 3(47):429-466, 1985). Raines clearly teaches that while "in EAE, unequivocal roles for T- and B-cells are well documented...In multiple sclerosis, immune mediation remains a contested area although several lines of indirect evidence for autosensitization to myelin exist..." (see page 430, second column, middle of page). Raines further teaches that "it must be emphasized that the most common form of EAE is an acute often fatal syndrome with little similarity to multiple sclerosis as a whole.." (page 431, first column, first full paragraph). Further, Alvord et al. (Annals Neurology, 6(6):461-468, 1978) set forth numerous differences between the EAE model and MS in humans (see for example Page 462, paragraph bridging columns 1-2, page 462, second column, last paragraph, and page 464, section entitled "Applications to MS"). Taken in context, the teachings of Alvord et al. and Traugott et al. (J. Neurosciences, 56:65-73, 1982) simply suggest that the EAE model is the best model currently available for studying potential therapies for MS. Thus it is clear that, while EAE is a useful experimental model of myelin-associated disease, it is not readily accepted by those skilled in the art as sufficiently correlative to human disease without additional evidence. Weiner et al. (Science, 259:1321-1324, 1993) sets forth the results from a clinical trial of oral tolerance for treating multiple sclerosis. In Weiner et al., the authors clearly state that "although conclusions about efficacy cannot be drawn from these data, they open an area of investigation for MS and other autoimmune diseases" (see Abstract). The authors further state that "it must be emphasized that this study does not demonstrate efficacy of oral myelin in the treatment of MS. Nonetheless, our data open an area of clinical investigation for the treatment of MS and other cell-mediated

organ-specific autoimmune diseases" (see page 1323, third column, last paragraph of article). These same conclusions are reached by Yoon (Science, 259:1263, 1993) in reviewing the Weiner et al. reference. Yoon states that "they [Weiner et al.] found tantalizing signs of improvement in some of the treated patients, but the results were not statistically significant and it's still far too early to say whether the treatment works" (see page 1263, first column, first paragraph). Thus it is clear from the above discussion and references that those of ordinary skill in the art would not readily accept the data set forth in Applicants' specification as sufficient to establish the enablement for treatment or therapy in humans using mouse models of multiple sclerosis, absent convincing factual evidence to the contrary. Here Applicants have not provided sufficient evidence to overcome the teachings of the art and establish a sufficient correlation between the rodent animal models used in the instant application and the clinical efficacy for treating demyelinating diseases or promoting remyelination in humans, as is clearly encompassed by the claims. Thus, there is insufficient evidence that the EAE model is an acceptable animal model for human therapeutics for that which is claimed. The Court has indicated that "inherent in the concept of the 'standard experimental animal' is the ability of one skilled in the art to make the appropriate correlations between the results actually observed with the animal experiments and the probable results in human therapy." In re Hartop and Brandes, 135 USPQ 412 at 426 (CCPA 1962). However, as set forth above there is ample evidence to question the use of the EAE animal model (see Paper No. 20, page 4, line 5-page 5, line 10). Thus, in the absence of convincing objective evidence to the contrary, the enabling disclosure is not commensurate in scope with the claims.

As to claims 1-4 and 9-14 and 19, the specification is not enabled for the pharmaceutical use of monoclonal antibodies 01, 04, A2B5, HNK-1, and natural or synthetic autoantibodies

having the characteristics thereof. Applicant clearly teaches that the aforementioned antibodies have different antigen binding specificities (page 10) and are encoded by different germline genes and thus do not possess the characteristics of SCH94.03 and SCH94.32. Thus, the skilled artisan would have substantial reason to doubt that these monoclonal antibodies would exhibit the same functional properties as SCH94.03 and SCH94.32. Moreover, Avrameas et al (PTOL-1449 reference AE; Molecular Immunology, 30(12):1133-1142, 1993) teach that natural autoantibodies have extensive polyreactivities and despite it polyreactivity, it is prone to react preferentially with one structure rather than another. Hartman et al (Molecular Immunology 26(4):359-370, 1989; PTOL-1449, reference BA) emphasizes that although the natural autoantibodies were polyreactive, and that the polyreactivity exhibited was unique for each natural autoantibody and were not indiscriminate (see abstract). The specification fails to teach that these "natural autoantibodies" have the same fine specificity and polyreactivity and thus one of skill in the art would not a priori predict that the function the same. Inasmuch as, the effectiveness of an antibody is presumably via its antigen combining region, one of skill in the art would have ample reason to doubt that the other instantly claimed antibodies would exhibit the same functional characteristics (i.e. promote remyelination, treat demyelination) as SCH94.03 and SCH94.32 in the murine host. Thus, the claim is not commensurate in scope with the enabling disclosure.

In view of the lack of predictable and reproducible correlation of the animal models with therapeutics in human disease, the lack of working examples commensurate in scope with the claimed subject matter, the skilled artisan would be forced into undue experimentation to practice the invention as is broadly claimed.

12. Claims 1-4, 10-14, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are rendered indefinite due to the use of the term "active fragment thereof". The biological activity of antibodies are multifold, because functions are elicited by both the antigen combining region and the Fc region. Thus, it is not clear which activity is being claimed. The examiner suggests language such as: antigen binding fragment thereof or epitope binding fragment thereof to clarify this point.

***Claim Rejections - 35 USC § 102 or 103***

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

15. The prior art date assigned the application is the instant filing date of 8/8/96 because the scope of the instant claims in regard to "mammal" and monoclonal antibodies was not enabled in the parent application. In order to be granted the priority date of a parent application, the parent must fully enable the scope of the claimed invention. The scope of the contemplated therapeutic monoclonal antibody was clearly not provided for in the parent application, as evidence by a complete lack of written description of the antibodies HNK-1, 01, 04, A2B5 and other natural or synthetic autoantibodies. Moreover, the parent specification was not enabled for therapy for the scope of "mammal". The enabling teachings of the parent specification are limited to murine, for reasons set forth above.

16. Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by Kasai et al (Brain Research, 227:155-158, 1983).

Kasai et al teach the monoclonal antibody A2B5. This monoclonal antibody is identical to the antibody recited in claim 19 and therefore anticipates the composition claim.

17. Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by Gard et al (Neuron, 5:615-625, 1990).

Gard et al teach the monoclonal antibodies A2B5, 01 and 04. These monoclonal antibodies are identical to the antibodies recited in claim 19 and therefore anticipates the composition claim.

18. Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by Fredman et al (Archives of Biochemistry and Biophysics, 233(2):661-666, 1984).

Fredman et al teach the monoclonal antibody A2B5. This monoclonal antibody is identical to the antibody recited in claim 19 and therefore anticipates the composition claim.

19. Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by Eisenbarth et al (Proc. Natl. Acad. Sci., 76(10):4913-4917, 1979).

Eisenbarth et al teach the monoclonal antibody A2B5. This monoclonal antibody is identical to the antibody recited in claim 19 and therefore anticipates the composition claim.

20. Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by Bansal et al (Journal of Neuroscience Research, 24:548-557, 1989).

Bansal et al teach the monoclonal antibodies 01 and 04. These monoclonal antibodies are identical to the antibodies recited in claim 19 and therefore anticipates the composition claim.

21. Claims 1-4, 9 and 11-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Miller et al (J. Neurosci., 14:6230-6238, 1994).

Miller et al teach that administration of the antibody SCH94.03 was found to promote central nervous system remyelination and therefore inherently treat demyelinating disease in mice infected chronically with Theiler's murine encephalomyelitis virus.

22. Those reference cited but not provided are of record on the PTOL-1449.

***Status of Claims***

23. No claims are allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to

reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application should be directed may be submitted to Group 1800 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The FAX number for Art Unit 1818 is (703) 308-4242.

Patricia A. Duffy, Ph.D.
September 30, 1997

Patricia A. Duffy, Ph.D.
Patent Examiner
Group 1800